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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,823	12/20/2006	Mladen Mercep	PL537	2037

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EXAMINER	
JARRELL, NOBLE E	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
12/16/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/587,823	MERCEP ET AL.	
	Examiner	Art Unit	
	NOBLE JARRELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/06;7/18/08;8/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I in the reply filed on 10/01/2008 is acknowledged. Groups I and II are merged into a single group.

Claim Objections

2. Claims 1-15 are objected to because of the following informalities: they contain non-elected subject matter. Variable X can be O or S. Appropriate correction is required. In claim 1, it appears that a comma is intended to exist between "optionally substituted C_1-C_7 alkyl" and "C_1-C_7 alkyloxycarbonyl". If the examiner's interpretation is wrong, applicants are encouraged to clarify the claims.

Information Disclosure Statement

3. The information disclosure statement filed 7/28/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Documents 2-4 have not been filed, and therefore have not been considered by the examiner.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for salts of compounds of formula I, does not reasonably

provide enablement for solvates of compounds of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of treating disorders, damage, or disease(s) linked to modulation of biogenic amines or neurotransmitters with compounds composed of a dibenzo[*b,f*]thieno[3,2-*d*]oxepine or dibenzo[*b,f*]thieno[3,2-*d*]thiepine ring which is further fused with C_6 ring. Thus, the claims taken together with the specification imply that compounds of the instant invention can treat ailments caused by the equilibrium of biogenic amines or neurotransmitters.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Vippagunta et al. (*Advanced Drug Delivery Reviews*, **2001**, *48*, 3-26, cited in IDS) teach that solvate or hydrate formation is unpredictable because each compound (even within a series of related compounds) responds uniquely to solvate or hydrate formation (page 18, section 3.4).

(5) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of solvates.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for preparation of salts of compounds of formula I.

However, the specification does not provide guidance for preparation of solvates of compounds of formula I.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-15 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

6. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* binding of compounds of formula I to 5-HT_{2a}, 5-HT_{2c}, and σ1 receptors, does not reasonably provide enablement for treatment of ailments linked to equilibrium of biogenic amines or neurotransmitters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*,

858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of treating disorders, damage, or disease(s) linked to modulation of biogenic amines or neurotransmitters with compounds composed of a dibenzo[*b,f*]thieno[3,2-*d*]oxepine or dibenzo[*b,f*]thieno[3,2-*d*]thiepine ring which is further fused with C_6 ring. Thus, the claims taken together with the specification imply that compounds of the instant invention can treat ailments caused by the equilibrium of biogenic amines or neurotransmitters.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Nitu et al. (*Expert Opinion in Investigational Drugs*, **2003**, *12(4)*, 545-59) teach that that topiramate, a glutamate (a neurotransmitter) antagonist, does not show efficacy in phase III clinical trials, and thus cannot work *in vivo* (section 3.3.4). This paper shows that even though a compound may work effectively *in vitro*, that does not necessarily guarantee that the compound will work *in vivo*.

Bhatt et al. (*Expert Opinion in Investigational Drugs*, **2007**, *16(8)*, 1197-1207) teach there is no *in vitro* model for glutamate inhibition that ensures clinical success (page 1203, section 5, paragraph 3).

Serretti et al. (*Expert Opinion in Therapeutic Targets*, **2004**, *8(1)*, 15-23) teach that 5-HT_{2c} receptors cannot be considered to be a potential target drug target for mood disorders (section 8, page 20).

Wood (*Expert Opinion in Investigational Drugs*, **2002**, *11(4)*, 457-67) teaches that inhibition of 5-HT receptors, although it may work *in vitro*, may not work *in vivo* (inhibition is not shown to be efficacious) (page 461, section 3.2).

(5) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in modulation of biogenic amines and neurotransmitters.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for *in vitro* binding of compounds of formula I to 5-HT_{2a}, 5-HT_{2c}, and σ1 receptors.

However, the specification does not provide guidance for treatment of disorders linked to equilibrium of biogenic amines or neurotransmitters.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-15 and the high unpredictability in the art as evidenced therein, and the lack

of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 4 does not satisfy the written description requirement because the claim relates to both inhibition and agonism of biogenic amines and neurotransmitters, as well as the storage, metabolism, and the reabsorption of biogenic amines or neurotransmitters. It is unclear whether or not storage, metabolism, and the reabsorption of biogenic amines or neurotransmitters, is considered to be inhibitory or agonism, or both.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1, what specific disease(s), damage, or disorder(s) is/are being treated? It is unclear what ailment is being treated. In terms of the biogenic amines, it is unclear what biogenic amines and neurotransmitters are targeted. MeSH ("Biogenic Amines", "Biogenic Monoamines", and "Biogenic Polyamines", http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi?mode=&term=Biogenic+Amines&field=entry, accessed December 6, 2008; "Neurotransmitter Agents", http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi, accessed December 6, 2008, both attached as PDF documents) lists several types of biogenic amines and neurotransmitters. In claim 4, it is

unclear whether or not storage, metabolism, and the reabsorption of biogenic amines or neurotransmitters, is considered to be inhibitory or agonism, or both.

Double Patenting

10. Claim 7 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 6. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 7 is considered a duplicate of claim 6 because the binding affinity does not carry any patentable weight, but is a functional limitation.

11. Claims 8 and 9 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 8 and 9 are considered duplicates of claim 1 because binding affinity does not carry any patentable weight (and is considered a functional limitation consequently).

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624